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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/616,141	07/08/2003	Heinz Pauls	USA3676 US CNT	9919
5487 7590 02/16/2007 ROSS J. OEHLER SANOFI-AVENTIS U.S. LLC 1041 ROUTE 202-206 MAIL CODE: D303A BRIDGEWATER, NJ 08807			EXAMINER WARD, PAUL V	
			ART UNIT 1624	PAPER NUMBER
SHORTENED STATUTORY PERIOD OF RESPONSE		NOTIFICATION DATE	DELIVERY MODE	
3 MONTHS		02/16/2007	ELECTRONIC	

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 02/16/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPatent.E-Filing@sanofi-aventis.com
andrea.ryan@sanofi-aventis.com

Office Action Summary

Application No.

10/616,141

Applicant(s)

PAULS ET AL.

Examiner

PAUL V. WARD

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 October 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 36-63 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 36-46 and 55 is/are allowed.
- 6) ☒ Claim(s) 47-54 and 56-63 is/are rejected.
- 7) ☒ Claim(s) 36 and 43 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Response to Arguments Regarding

Claim Rejections - 35 USC § 112

1. The rejections, of claims 36-42 and 19-34, cited in the Office Action dated May 9, 2006, have been overcome by Applicant's amendment in the reply filed October 3, 2006.

Claim Objections

2. Examiner suggests that Applicant submit a larger font for the ring system substituents in Claim 36, and for the compounds in claim 43.

Election/Restrictions/Rejoinder

3. Claims 36-46 are directed to an allowable product. Pursuant to the procedures set forth in MPEP § 821.04(B), claims 47-63, directed to the process of making or using an allowable product, previously withdrawn from consideration as a result of a restriction requirement, are hereby rejoined and fully examined for patentability under 37 CFR 1.104.

Because all claims previously withdrawn from consideration under 37 CFR 1.142 have been rejoined, **the restriction requirement as set forth in the Office action mailed on September 20, 2005 is hereby withdrawn.** In view of the withdrawal of the restriction requirement as to the rejoined inventions, applicant(s) are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over

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the claims of the instant application. Once the restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 48-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for “treating”, does not reasonably provide enablement for “preventing”. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. Applicant is entitled to treatment or treating, not “prevention” or “preventing”.
5. Claims 47-54 and 56-63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention without undue experimentation.

Claims 47-54 and 56-63 are directed to a method of treating inflammatory disease associated with tryptase activity and Factor Xa activity, chronic asthma, arthritis, ocular conjunctivitis, inflammatory bowel disease, lung disease, fibrosis, liver

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cirrhosis, myocardial fibrosis, hypertrophic scars dermatitis, psoriasis, stroke, angina, periodontal disease, tumor growth, ulcers and viral infections diseases. In light of this, it can be asserted that in spite of the vast expenditure of human and capital resources in recent years, no one drug has been found which is effective in treating all types of treating inflammatory disease associated with tryptase activity and Factor Xa activity, chronic asthma, arthritis, ocular conjunctivitis, inflammatory bowel disease, lung disease, fibrosis, liver cirrhosis, myocardial fibrosis, hypertrophic scars dermatitis, psoriasis, stroke, angina, periodontal disease, tumor growth, ulcers and viral infections diseases. In re Hozumi, 226 USPQ 353 (ComrPats 1985).

The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue".

These factors include, but are not limited to:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims

The breadth of the instant claims is seen to encompass methods for treating inflammatory disease associated with tryptase activity and Factor Xa activity, chronic asthma, arthritis, ocular conjunctivitis, inflammatory bowel disease, lung disease, fibrosis, liver cirrhosis, myocardial fibrosis, hypertrophic scars dermatitis, psoriasis, stroke, angina, periodontal disease, tumor growth, ulcers and viral infections by administering to a patient in need of such treatment a therapeutically effective amount of the compound claim. Applicant failed to exactly defined what types of neurodegenerative diseases are treated. Thus, the claims are extremely broad.

The nature of the invention

The nature of the invention is the treatment of inflammatory disease associated with tryptase activity and Factor Xa activity, chronic asthma, arthritis, ocular conjunctivitis, inflammatory bowel disease, lung disease, fibrosis, liver cirrhosis, myocardial fibrosis, hypertrophic scars dermatitis, psoriasis, stroke, angina, periodontal disease, tumor growth, ulcers and viral infections through the use of the claimed compound and derivatives thereof. Currently, there are no known agents that treat Alzheimer's and neurodegenerative diseases all inclusively.

The level of predictability in the art

The treatment of inflammatory disease associated with tryptase activity and Factor Xa activity, chronic asthma, arthritis, ocular conjunctivitis, inflammatory bowel disease, lung disease, fibrosis, liver cirrhosis, myocardial fibrosis, hypertrophic scars dermatitis, psoriasis, stroke, angina, periodontal disease, tumor growth, ulcers and viral infections is highly unpredictable. It is well established that "the scope of enablement

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varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The amount of direction provided by the inventor.

The applicant has not demonstrated sufficient guidance provided in the form of administration profiles, combination ratios of the active agents or reference to the same in the prior art to provide a skilled artisan with sufficient guidance to practice the instant treatment of inflammatory disease associated with tryptase activity and Factor Xa activity, chronic asthma, arthritis, ocular conjunctivitis, inflammatory bowel disease, lung disease, fibrosis, liver cirrhosis, myocardial fibrosis, hypertrophic scars dermatitis, psoriasis, stroke, angina, periodontal disease, tumor growth, ulcers and viral infections claimed. Further, the applicant discloses that an effective amount of the compound will be administered (see specification) without providing any direction other than that the compounds of the invention have a high therapeutic index and follows this with a definition readily found in a basic pharmacology textbook. It should be noted that the therapeutic index of a drug in humans is almost never known and is only determined through clinical experience.

The existence of working examples.

There is not seen in the disclosure, sufficient evidence to support Applicant's claims of treating inflammatory disease associated with tryptase activity and Factor Xa activity, chronic asthma, arthritis, ocular conjunctivitis, inflammatory bowel disease, lung disease, fibrosis, liver cirrhosis, myocardial fibrosis, hypertrophic scars dermatitis,

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psoriasis, stroke, angina, periodontal disease, tumor growth, ulcers and viral infections.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 27 USPQ2d 1510 (CAFC). The disclosure does not demonstrate sufficient evidence to support the applicant's claim to the treatment and methods in inhibition. There are not sufficient working examples or data from references of the prior art to provide a nexus between those examples and a method of treating inflammatory disease associated with tryptase activity and Factor Xa activity, chronic asthma, arthritis, ocular conjunctivitis, inflammatory bowel disease, lung disease, fibrosis, liver cirrhosis, myocardial fibrosis, hypertrophic scars dermatitis, psoriasis, stroke, angina, periodontal disease, tumor growth, ulcers and viral infections with the claimed compound.

The level of one of ordinary skill.

The level of skill is that of one with a doctoral understanding of inflammatory disease associated with tryptase activity and Factor Xa activity, chronic asthma, arthritis, ocular conjunctivitis, inflammatory bowel disease, lung disease, fibrosis, liver cirrhosis, myocardial fibrosis, hypertrophic scars dermatitis, psoriasis, stroke, angina, periodontal disease, tumor growth, ulcers and viral infections therapeutics.

The quantity of experimentation.

A great deal of experimentation is required. In order for there to be a method of treating inflammatory disease associated with tryptase activity and Factor Xa activity,

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chronic asthma, arthritis, ocular conjunctivitis, inflammatory bowel disease, lung disease, fibrosis, liver cirrhosis, myocardial fibrosis, hypertrophic scars dermatitis, psoriasis, stroke, angina, periodontal disease, tumor growth, ulcers and viral infections generally, as claimed by the applicant, it would be necessary to show that a vast range of different types of inflammatory disease associated with tryptase activity and Factor Xa activity, chronic asthma, arthritis, ocular conjunctivitis, inflammatory bowel disease, lung disease, fibrosis, liver cirrhosis, myocardial fibrosis, hypertrophic scars dermatitis, psoriasis, stroke, angina, periodontal disease, tumor growth, ulcers and viral infections. Furthermore, direction, in the form of examples, must be shown to determine what an effective dose may be. The references submitted do not demonstrate this. Therefore, one of ordinary skill in the art would require a significant amount of experimentation in order to determine the effective dosage to treat the multitudes of different types of inflammatory disease associated with tryptase activity and Factor Xa activity, chronic asthma, arthritis, ocular conjunctivitis, inflammatory bowel disease, lung disease, fibrosis, liver cirrhosis, myocardial fibrosis, hypertrophic scars dermatitis, psoriasis, stroke, angina, periodontal disease, tumor growth, ulcers and viral infections with the claimed compound individually or in combination with other therapeutic agents.

Thus, it can be safely concluded that the instant case fails to provide an enabling disclosure for the treatment of inflammatory disease associated with tryptase activity and Factor Xa activity, chronic asthma, arthritis, ocular conjunctivitis, inflammatory bowel disease, lung disease, fibrosis, liver cirrhosis, myocardial fibrosis, hypertrophic

scars dermatitis, psoriasis, stroke, angina, periodontal disease, tumor growth, ulcers and viral infections.

Conclusion

The compounds, and the pharmaceutical composition in Claims 36-46 and 55 were not found to be obvious nor anticipated by the prior art of record. The prior art does not teach or suggest the 1-aroyl-piperidinyl benzamidine compounds substituted in the manner in the presently claimed compounds. Therefore, these claims are allowable.

Claims 36-63 are pending. Claims 47-54 and 56-63 are rejected. Claims 36-46 and 55 are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

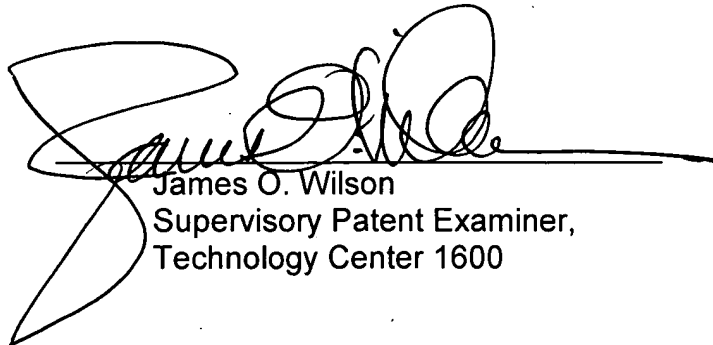
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to PAUL V WARD whose telephone number is 571-272-2909. The examiner can normally be reached on M-F 8 am to 4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



James O. Wilson
Supervisory Patent Examiner,
Technology Center 1600